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09/823,699	03/30/2001	Munehide Kano	50026/022002	7451

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 01/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,699	KANO ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed November 14, 2002 has been entered as Paper #13. Claims 1, 2, 9, 10, and 11 have been amended, claims 12-45 are newly added. Claims 1-45 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in paper #13 would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 stand rejected and the rejection has been modified and applies to new claims 12-45 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a Sendai viral vector expressing a viral protein of an immunodeficiency virus, and using a Sendai virus encoding a gag or gag-pol fusion protein for inducing a specific immune response via intranasal administration and/or combined with a DNA vector expressing the genome of the immunodeficiency virus, does not reasonably provide enablement for vaccination with Sendai viral vector via any route of administration. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In paper #13, applicants argue that the examiner acknowledges that the method is enabled for *in vivo* by intranasal administration, that the levels of the skilled in the field is high, that routine challenge models were available, that Ourmanov or McCluskie reference is not relevant to the state of the Sendai virus vaccine.

The arguments have been fully considered but found not persuasive for reasons of record and the following.

The independent claims still embrace any route of administration, and are not limited to intranasal administration. The Sendai virus as an RNA virus has a natural tropism to respiratory epithelium, and theoretically would rapidly degraded if introduced to blood circulation, thus, it is highly unpredictable whether other routes of administration for a Sendai virus would induce a specific immune response.

Ourmanov et al (J. Virol. 2000;74:2740-2751, IDS) teach AIDS vaccine in general, and *McCluskie et al* (Mol Med 1999 May;5:287-300) teach the importance of route of administration with the type of immune response induced, therefore, they are relevant to the instantly claimed invention.

Further, although claims 9 and 10 have been amended, applicants fail to address the following issue raised in the Office action, which will be reiterated as following: "the specification fails to teach whether the SeV-SIV-Gag induced changes in CD8+ cells is sufficient to elicit a protective response against SHIV, whether SeV-SIV-Gag alone (without a previous DNA vaccine encoding the viral protein of HIV or SIV could achieve

any protective effect against SHIV infection either in monkeys or in humans, and whether the protective effect obtained in the DNA-RNA combination regimen is attributed, solely or predominantly, to the DNA vaccine. The specification fails to provide sufficient guidance for the skilled artisan to practice the invention without undue experimentation.

For the reasons of record and those set forth above, the instant specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. §112, 1st paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 8, 17, 22, 23, 35, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the conflicting claim recitation, "inoculated at least once in multiple vaccine inoculation". "At least once" encompasses one inoculation, whereas a multiple vaccine regimen requires multiple inoculations. When the art of record such as *Flanagan et al* immunized the mice once, it is unclear whether the claims encompass or exclude the art, thus, the metes and bounds of the claims are unclear. For the purpose of a compact prosecution, the claims will be interpreted as more than once immunization.

Claim 17 recites the limitation "vaccine" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5-10, 16-18, 20-45 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Flanagan et al* (J Gen Virol 1997;78:991-7) or *Seth et al* (PNAS 1998;95:10112), in view of *Hurwitz et al* (Vaccine 1997;15:533-40).

These claims are drawn to a composition comprising a Sendai virus vector (Sev) vaccine encoding a viral protein of an immunodeficiency virus selected from a Gag-pol fusion protein or a gag protein and a method of using such for vaccination in an animal, wherein the vaccine is inoculated intranasally for more than one time, wherein the method comprises first inoculating a DNA vaccine comprising a DNA encoding the genome of an immunedeficiency virus and then inoculating the Sendai virus vector. wherein said genome is defective in env and nef gene, wherein the animal is a mammalian, a non-human primate, or a human.

Flanagan et al teach a method of using a recombinant adenovirus expressing SIV Gag protein (a DNA vaccine without env or nef gene) for vaccination in mice and achieved long-lasting immune response by intranasal inoculation. *Flanagan et al* go on

to teach that although both the Env and Gag could serve as an antigen for HIV vaccine, the variability of the *env* gene makes the Env protein a difficult antigen for a vaccine to target, whereas more conserved Gag protein is a potent stimulator of both the cellular and humoral components of the immune system and may contain important protective epitopes (2nd paragraph on left column in page 992). On the other hand, they teach that single epitope Gag-specific CTL activity cannot prevent infection by SIV (last paragraph). When commenting on the route of administration, *Flanagan et al* teach mucosal route of delivery is desired for HIV vaccine because "IT CAN STIMULATE LOCAL IMMUNE RESPONSES THAT COULD BE OF VALUE IN PROTECTING AGAINST VIRUSES SUCH AS HIV WHICH ALSO INFECT VIA THIS ROUTE" (paragraph bridging the left and right column, page 996). *Flanagan et al* do not use a Sendai virus vector or a gag-pol fusion protein.

Seth et al teach using a vaccinia virus vector expressing gag-pol fusion polypeptides (a DNA vaccine without env or nef gene) in multiple dosages (day 1 and 126) and inducing cytotoxic immune response specific to gag pol proteins in a rhesus monkey. *Seth et al* teach, " WITH ACCUMULATING EVIDENCE THAT VIRUS-SPECIFIC CYTOTOXIC T LYMPHOCYTES (CTLS) ARE IMPORTANT IN CONTAINING THE SPREAD OF HIV-1 IN INFECTED INDIVIDUALS, A CONSENSUS HAS EMERGED THAT AN HIV-1 VACCINE SHOULD STIMULATE THE GENERATION OF CTLS". (1st paragraph, page 10112)

Hurwitz et al teach intranasal multiple inoculation of a Sendai virus vaccine expressing human parainfluenza virus-1 (hPIV-1) in African green monkeys (abstract, figures 1-4, and table 1). They teach that Sendai virus could easily be administered intranasally, could induce immune response that is similarly cross reactive with hPIV-1, yet would not cause ill effect, and induced protective effect against a subsequent

challenge (Introduction, page 533). *Hurwitz et al* suggest that the data from their report in conjunction with previous work encouraging further testing of Sendai virus as a potential human vaccine because its long-lasting effect stimulating memory B-cells as well as CTL response (last paragraph, page 539).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Flanagan et al*, or *Seth et al*, and *Hurwitz et al*, by substituting and/or combining the recombinant adenoviral or vaccinia vector with a Sendai viral vector with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the recited DNA vaccine such as adenoviral and vaccinia expressing a gag pol have been proven effective in inducing an immune response to HIV or SIV, and as *Flanagan et al* taught, gag protein alone may not elicit a protective response, and that mucosal route, thus viral vectors have mucosal tropism such as Sendai viral vector, is suitable for developing a HIV or SIV vaccine. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-10, and 16-45 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Flanagan et al* (J Gen Virol 1997;78:991-7) or *Seth et al* (PNAS 1998;95:10112), and *Hurwitz et al* (Vaccine 1997;15:533-40) as applied to claims 1, 2, 5-10, 16-18, 20-45 above, and further in view of *Yu et al* (Genes Cells. 1997 Jul;2:457-66).

Claims 4, 5, and 19 are further drawn to a Sendai viral vector defective in V gene. The combined teachings of *Flanagan et al*, or *Seth et al*, and *Hurwitz et al*, do not teach such a vector.

Yu et al teach a Sendai virus vector defective in V gene encoding a virus protein of the human immunodeficiency virus, and that the deletion of the nonessential V gene leads to greater expression of a viral protein (abstract). *Yu et al* go on to teach that they established the fact that Sendai virus has a broad host range, thus, allowed gp120 expression in all three natural host cells for HIV-1, i.e. primary blood mononuclear cells, macrophages, or established T cell lines.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the vector taught by *Yu et al*, in the process taught by *Flanagan et al*, or *Seth et al*, and *Hurwitz et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the vector because increased production of the viral protein would have enhanced the vaccine effect and because Sev is known to be sufficient in transducing the natural host cells for HIV, thus, useful for HIV vaccine development. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In paper #13, applicants argue that it appears that Flanagan et al satisfied with the vectors that they had in hand, there is no suggestion that their vector could be improved. The argument is not persuasive because as shown in the combined teachings of *Flanagan et al*, or *Seth et al*, and *Hurwitz et al,* the skilled artisan would use different vectors and different antigenic epitopes to develop an ideal vaccine for

immunodeficiency virus. As taught by *Hurwitz et al and Yu et al,* Sendai virus vectors are efficient in transducing natural host cells of HIV or SIV, whereas the natural tissue tropism for adenovirus is liver cells. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Claims 11-13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Flanagan et al* (J Gen Virol 1997;78:991-7), and *Seth et al* (Proc Natl Acad Sci USA 1998;95:10112-6), in view of *Kast et al* (J Immunol 1988;140:3186-93, IDS), and *Yu et al* (Genes Cells. 1997 Jul;2:457-66).

This claim is drawn to a method for inducing cellular immune response to a viral protein of an immunodeficiency virus in vitro comprising (a) introducing a Sendai virus vector encoding said viral protein into an antigen-presenting cell, (b) contacting the APC with a T helper cell and a cytotoxic T cell.

Flanagan et al teach the *in vitro* CTL assay, wherein a viral vector encoding a gag protein is introduced to APCs (splenocytes, stimulator cells) in the presence of a Th and Tc cells (splenocytes from immunized mice, responders), and a cellular immune response specific to a SIV gag is induced (CTL-assays, page 992).

Seth et al teach that the gag pol fusion protein could also induce CTL (abstract) and they use autologous B lymphblastoid cells as APCs.

Kast et al teach a method comprising introducing a Sendai virus to dendritic cell (APC) (left column, page 3187), the transfected DCs are then capable of presenting the antigen to T cells inducing cytotoxic T lymphocyte activity. *Kast et al* do not teach a Sendai virus encoding HIV derived protein.

Yu et al teach a Sendai virus vector encoding a virus protein (gp120) of the human immunodeficiency virus. *Yu et al* also teach that the vector system is active in mononuclear cells (T cells) and macrophage (APCs) and the vector could be used in immunological studies (abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Flanagan et al* and *Kast et al*, by simply employ the vector taught by *Yu et al* and the viral protein taught by *Seth et al* with a reasonable expectation of success in inducing a specific cellular immune response. The ordinary skilled artisan would have been motivated to modify the method for their particular needs of investigation, i.e. a particular vector of interest, or a particular antigen of interest, etc. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Flanagan et al* (J Gen Virol 1997;78:991-7), *Seth et al* (Proc Natl Acad Sci USA 1998;95:10112-6), *Kast et al* (J Immunol 1988;140:3186-93, IDS), and *Yu et al* (Genes

Cells. 1997 Jul;2:457-66) as applied to claims 11-13, and 15 above, further in view of *Boutillon et al* (US 6,015,564).

Claim 14 is drawn to using an autologous herpesvirus papio-immortalized B lymphoblastoid cell as the APC.

Seth et al teach using autologous B lymphoblastoid cells (4th paragraph, left column, page 10113), but not immortalized cells.

Boutillon et al teach using herpes virus papio transforming B lymphoblastoid cells for CTL assay.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Flanagan et al, Seth et al,* and *Kast et al, and Yu et al*, by simply employ immortalized cells as taught by *Boutillon et al* with a reasonable expectation of success in inducing a specific cellular immune response. The ordinary skilled artisan would have been motivated to modify the method because the immortalized cells would be easier to care for. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
January 27, 2003

ANNE M. WEHBE
PRIMARY EXAMINER